Cardiopulmonary bypass: Evidence or experience based?

Claus Bartels, MD, Anja Gerdes, MD, Jörg Babin-Ebell, MD, Friedhelm Beyersdorf, MD, Udo Boeken, MD, Torsten Doenst, MD, Peter Feindt, MD, Michael Heiermann, MD, Christian Schlensak, MD, and Hans-Hinrich Sievers, MD

Dr Bartels

See related editorial on page 11.

Objective: Evidence-based medicine is emerging as a new paradigm for medical practice. The purpose of this study was to evaluate the amount and quality of scientific evidence supporting principles that are currently applied for cardiopulmonary bypass performance.

Methods: A survey of all German departments of cardiac surgery regarding cardiopulmonary bypass performance disclosed major differences. Consequently, for 48 major principles of cardiopulmonary bypass performance, relevant Medical Subject Headings were identified, and a literature search of the Medline database was performed. Two sequentially applied sets of inclusion-exclusion criteria were selected to assess the best available evidence.

Results: Thirty-three thousand articles relating to the subject were identified. Among these, 1500 fulfilled the first set of inclusion criteria: meta-analysis of (randomized) controlled clinical trials and in vitro and animal studies. Rigorous methodological criteria were then applied to further select remaining publications. Ultimately, 225 articles referring to major cardiopulmonary bypass principles were identified as providing the best available evidence. These were graded according to their methodological rigor (susceptibility to bias). The scientific evidence on the investigated cardiopulmonary bypass principles did not prove to be of a high enough level to allow general recommendations to be made.

Conclusions: The scientific data concerning the effectiveness and safety of key principles of cardiopulmonary bypass are insufficient in both amount and quality of scientific evidence to serve as a basis for practical, evidence-based guidelines.

The first successful clinical application of cardiopulmonary bypass (CPB) by John Gibbon in 1953 revolutionized cardiac surgical procedures. Today, CPB is routinely used for various cardiac and noncardiac surgical operations and appears to be a safe procedure. However, the unresolved problems and limitations of CPB are obvious in daily clinical practice. Bleeding disorders, systemic inflammatory reactions, multiorgan failure, neurologic deficits, permanent intellectual impairment, and pulmonary dysfunction are only some examples of the hazards of modern CPB.

Improving the quality of medical care by establishing medical practice guidelines has been vigorously promoted by the US health care system.[1] The responsible medical societies have developed practice guidelines on the basis of evidence-based medicine criteria for various procedures.[2-6] Thus a new paradigm of medical practice is emerging. Evidence-based medicine de-emphasizes intuition and unsys-

Written on behalf of the Working Group on Extracorporeal Circulation and Mechanical Ventricular Assist Devices of the German Society for Thoracic and Cardiovascular Surgery.

Received for publication March 9, 2001; revisions requested May 31, 2001; revisions received Sept 12, 2001; accepted for publication Oct 1, 2001.

Address for reprints: C. Bartels, MD, Clinic for Cardiac Surgery, Medical University of Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany.

J Thorac Cardiovasc Surg 2002;124:20-7

0022-5223/2002 $35.00+0 **12/1/121506**

doi:10.1067/mtc.2002.121506

tematic clinical experience as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical and experimental research.[7]

A survey concerning principles of CPB performance was sent to all German centers of cardiac surgery. The obtained results disclosed significant differences regarding CPB performance. As a consequence, the Working Group on Extra-Corporeal Circulation and Mechanical Ventricular Assist Devices of the German Society for Thoracic and Cardiovascular Surgery tried to develop a consensus document for the clinical application of CPB. Forty-eight major principles of CPB were formulated into questions to be addressed by a review of the scientific literature. The issues of interest covered nearly all relevant aspects of CPB (eg, optimum activated clotting time for routine CPB or during hypothermic circulatory arrest; anticoagulation management by the use of aprotinin; myocardial protection; technical safety aspects; pump flow rate, blood pressure, or both, for the different degrees of hypothermia; and washout of toxic metabolites from CPB material). In case of clinical studies, the key parameters for scientific evaluation of the investigated principles concentrated on patients' clinical outcomes and not on surrogate parameters.

Because it is impossible to deal adequately with each of the 48 questions within the scope of an article, the topics and our results are presented here in tabular form (Tables 1 and 2). As an example of our methodological approach, we selected a sample question (topics 38 and 39) that will be described in detail in the appropriate sections.

The sample question was, "What is the appropriate acid-base management strategy for optimum cerebral protection in adults with respect to moderate respiratory deep hypothermia?"

The clinical rationale behind this question was that neurologic injury and postoperative cognitive dysfunction appear to be the most frequent complications of CPB procedures. From 1970 to 1973, 8% of patients subjected to CPB died after a neurologic event; by contrast, from 1980 to 1983, 20% of postoperative deaths were related to severe neurologic injury.[8] More recently, a longitudinal assessment of neurocognitive function after coronary artery bypass grafting was reported.[9] These authors demonstrated an incidence of cognitive decline of 53% at discharge and of 42% after 5 years.

Although the cause of postoperative central nervous system dysfunction in patients subjected to CPB is multifactorial, microgaseous and solid emboli are particularly culpable and seem to be influenced by different brain perfusion rates of pH management.

Scientific and Pathophysiologic Background

The ability to control a patient's body temperature within a wide range is one of the most important therapeutic modalities made available by the application of CPB. One of the most frequently discussed aspects of clinical hypothermia is the appropriate acid-base management strategy during cooling and rewarming. The term *alpha-stat* indicates an acid-base management in which the net charge (dissociation) of proteins remains constant as the temperature changes. The alternative method is termed *pH-stat* (ie, maintaining pH value constant at varying temperatures).

Alpha-stat management will result in lower cerebral flow compared with pH-stat management. Intact cerebral autoregulation has been demonstrated in human subjects after alpha-stat strategy at temperatures from 21°C to 29°C.[10] In contrast, cerebral autoregulation was abolished, and it varied, depending on cerebral blood flow, when pH-stat was used.[11] In deep hypothermia the normal vascular responses are lost, and cerebral blood flow is dependent on the perfusion pressure with uncoupling of flow and metabolism. During moderate hypothermia, the variations in P_{CO_2} between the different acid-base managements are only minor and do not seem to be clinically relevant.[12] In contrast, the difference in P_{CO_2} during deep hypothermia approaches 80 mm Hg between the two acid-base strategies. The increased cerebral blood flow associated with pH-stat strategy may increase the risk of microemboli, cerebral edema, or high intracranial pressure. On the other hand, increased brain perfusion may result in improved cerebral cooling before circulatory arrest.

This article has two main aims: (1) to summarize the results obtained regarding the scientific quality of the reviewed publications and (2) to determine the scientific basis of currently applied CPB principles.

Methods

We performed a systematic search of the Medline database for Medical Subject Headings referring to the various principles of CPB in the past 20 years. The appropriate selection, combination, and use of the Medical Subject Headings were cross-checked by two other members of our working group to ensure as complete a search as possible.

Step 1: Scientific Level of the Reviewed Literature

All abstracts of articles identified by the search were reviewed by at least four members of the working group. Articles were selected for further review if one or more of the following criteria was met:

- Articles were available in English, French, Italian, or Spanish language
- Articles used a randomized study design
- A control group was available
- Articles were editorials and reviews in peer-reviewed journals
- Articles were meta-analyses
- The same criteria were applied to in vitro studies and animal studies

All reference lists were checked for publications missed in the Medline search.

CSP

TABLE 1. Summarized results

Subject	Scientific level of literature I	II	III	IV	Parameters determining clinical outcome	Class*
Technical equipment						
1. Centrifugal vs roller pump	0	4	1	0	sp, trans, vent, icu	IIb
2. Pulsatile vs nonpulsatile perfusion	0	5	7	0	sp, mort, mi, morb, neur	IIb
3. Heparin-coated surfaces	0	5	3	0	sp, trans, vent, icu, hosp, mort, morb, neur, arr, mi, vent	IIb
4. Toxicity of PVC	0	0	2	0	sp	III
5. Closed vs open cardiotomy reservoirs	0	1	2	1	sp, trans, icu, hosp	III
6. Arterial filter systems	0	0	6	0	sp, neur	III
7. Autotransfusion vs cell separation	0	1	1	1	sp, trans	IIb
Preparation of CPB						
8. Volume substitution before CPB	0	4	0	0	sp, trans	III
9. Priming in adults	0	10	1	0	sp, trans	IIb
10. Priming in infants and neonates	0	0	3	2	sp, trans	IIb
11. Application of aprotinin	3	1	2	0	sp, re, trans, mi, mort, all, byp	IIa
12. Additive drugs in priming solution	0	4	0	2	sp, cvi, vent	III
13. Temperature of priming solution	na	na	na	na		III
14. Perfusion volume	na	na	na	na		III
15. CO_2 rinsing of arterial filters	na	na	na	na		III
16. Protection of tubes by connectors	na	na	na	na		III
Performance and supervision of CPB						
17. How should ACT be measured?	0	2	0	3	sp	IIa
18. Other coagulation parameters besides ACT during CPB	0	5	7	0	sp, trans	III
19. Level of ACT during CPB	0	3	2	0	sp, trans	IIb
20. Level of ACT for hemodilution during CPB	0	1	1	2	sp, trans	III
21. Level of ACT with aprotinin during CPB	1	1	0	1	sp, byp	III
22. Level of ACT with aprotinin in DHCA	0	1	3	0	sp, trans, rf	III
23. Heparin administration	0	1	0	0	sp, trans	III
24. Heparin resistance	0	0	3	0	sp	IIb
25. Antithrombin III deficiency	0	0	3	0	sp, trans	IIa
26. Protamine application	0	2	2	0	sp, trans	IIb
27. Effects of priming solution on platelet function	0	2	0	0	sp, trans	III
28. Effects of oxygenator type on platelet function	0	1	4	0	sp, trans	III
29. Effects of pump type on platelet function	0	2	1	0	sp	III
30. Platelet-rich plasmapheresis and transfusion requirements	0	3	0	0	sp, trans	III
31. Desmopressin acetate and transfusion requirements	0	4	0	0	sp, trans	IIb
32. Indicators for platelet transfusion	0	1	3	0	sp, trans	III
33. Patient selection for tranexamic acid or ε aminocaproic acid treatment	0	5	3	0	sp, mi, cvi, pe, dvt, trans	IIb
34. Dosage of tranexamic acid or ε aminocaproic acid	0	2	0	0	sp, trans, cvi, dvt, mi	IIb
35. Effects of tranexamic acid or ε aminocaproic acid on bleeding	1	5	0	0	sp, trans, mi, cvi, mort	
a) in elective patients						IIb
b) in patients with increased risk of bleeding					sp, trans, cvi, mi, dvt	IIb
36. pH strategy during DHCA in pediatric cardiac surgery	0	1	2	2	sp, con, vent, icu, neur	IIa
37. pH strategy during moderate hypothermia in pediatric cardiac surgery	na	na	na	na		III
38. pH strategy during DHCA in adult cardiac surgery	na	na	na	na		III
39. pH strategy during moderate hypothermia in adult cardiac surgery	0	5	1	0	sp, mort, mi, cvi, arr, rf, neur, vent, icu	IIa
40. Myocardial protection	0	7	3	1	sp, mort, mi, cvi, rf, icu, vent	III

(Continued on next page)

TABLE 1. Cont'd

Subject	Scientific level of literature I	II	III	IV	Parameters determining clinical outcome	Class*
41. Optimum core temperature	0	10	1	0	sp, mort, mi, cvi, neur, re, trans, lco	III
42. Optimum temperature gradient	0	0	0	2	sp	III
43. Optimum mean arterial perfusion pressure and flow	0	2	4	0	sp, neur, mort, mi, cvi, qual	III
44. Selective cerebral perfusion	0	0	5	1	sp, mort, neur	III
45. Efficacy of different methods of selective cerebral perfusion	0	0	5	1		III
Documentation, quality assurance, personal resources						
46. Automatic data documentation	0	0	5	6	na	III
47. Quality assurance	0	0	3	11	na	III
48. Perfusionist's education	0	0	6	0	na	III

For complete abbreviation list, see Table 2. *na*, No scientific publication available.
* Classification of the scientific evidence of the examined principle.

Step 2

The scientific quality of the manuscripts was assessed by at least four members of the working group regarding structure and content.

Manuscripts were selected for further review if they included the following:

- A background review of the subject
- An explicit statement of objectives
- A detailed description of the type and selection of subjects and procedures
- A detailed description of applied methods
- A description of quantitative methods
- An exact description of the randomization procedure (eg, centralized, pharmacy controlled, prenumbered, or coded)
- An adequate description of executing or measuring the predictor-outcome variable
- A comparison with alternative technologies and procedures
- A detailed description of clinical end points

All articles that did not meet these criteria were checked for further important information, in which case they were also selected for review. If no article fulfilled the mentioned criteria, articles of lesser scientific quality were selected for review. Articles were excluded if any of the following were true:

- Study results were summarized in high-quality reviews selected for evaluation of their scientific level
- The same data had evidently been published twice
- The statistical methods were inadequate
- The selection of subjects, procedures, or both, was inadequate

Step 3

According to the methodological rigor, the selected articles were classified according to their scientific level:

- Level I: Investigations yielding clear evidence that a given procedure or treatment is useful and effective (large randomized prospective trials with low false-positive [α] and low false-negative [β] errors and high-quality meta-analysis)
- Level II: Investigations that do not provide clear scientific evidence about the usefulness, efficacy, or both of a procedure or treatment (eg, small sample size and lack of randomization)
- Level III: Investigations that do not provide scientific evidence about the usefulness, efficacy, or both, of a procedure or treatment (eg, trials without appropriate controls)
- Level IV: In vitro or animal studies and nonsystematic reviews

All in vitro and animal studies selected for inclusion in the study were classified as level IV without respect to the scientific design and the number and quality of interventions or statistical methods. This approach was chosen in view of the limited application of in vitro and animal study results to the clinical situation.

The level of scientific evidence assigned to each article was cross-checked by two other members of the working group. Any disagreements were resolved by means of consensus. For all arti-

TABLE 2. Abbreviations used in Table 1

trans	Transfusion requirements, including coagulation factors
mort	Mortality
morb	Morbidity
mi	Perioperative myocardial infarction
neur	Neurologic-cognitive dysfunction
byp	Bypass graft occlusion
rf	Renal failure
cvi	Cerebrovascular insult
pe	Pulmonary embolism
dvt	Deep venous thrombosis
con	Convulsion
arr	Arrhythmia requiring treatment
lco	Low cardiac output
re	Rethoracotomy for bleeding
vent	Ventilation dependence
icu	Intensive care unit stay
hosp	Hospital stay
all	Allergic shock
sp	Surrogate parameter
qual	Quality of life
DHCA	Deep hypothermic cardiac arrest
ACT	Activated clotting time

CSP

TABLE 3. Key word selection for the sample question

Key word 1	Key word 2	Articles identified
pH	0	226,167
pH management	0	1,481
pH management	Cardiopulmonary bypass	80
pH management	Extracorporeal circulation	95
pH management	Heart-lung machine	0
pH management	Cerebral blood flow	57
pH management	Temperature	146
pH management	Hypothermia	97
pH management	Hypothermic cardiac arrest	1
pH management	Hypothermic circulatory arrest	14
pH management	Cardiac surgery	26
pH management	Heart surgery	59
pH-stat	0	483
pH-stat	Cardiac surgery	15
pH-stat	Heart surgery	29
pH-stat	Extracorporeal circulation	53
pH-stat	Cardiopulmonary bypass	58
pH-stat	Heart-lung machine	1
pH-stat	Circulatory arrest	15
Alpha-stat	0	139
Alpha-stat	Cardiac surgery	24
Alpha-stat	Heart surgery	56
Alpha-stat	Extracorporeal circulation	100
Alpha-stat	Cardiopulmonary bypass	104
Alpha-stat	Heart-lung machine	1
Alpha-stat	Circulatory arrest	22

cles, the adequate use of statistical methods was critically assessed and discussed with collaborating medical statisticians, for example:

- Assurance of comparability of study groups
- Data analysis according to the primary study protocol
- Whether paired tests for paired data were used
- Differentiation between correlation and regression
- Correct calculation and interpretation of the correlation coefficient (*r* value)
- Correct calculation and interpretation of the *P* value

Step 4: Classification of the Scientific Evidence on CPB Principles

After all relevant articles had been graded with respect to their scientific level, the investigated principle (procedure or treatment) was classified according to a modification of the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for scientific evidence.[2,4,6]

- Class I: Principle for which there is clear evidence, scientific agreement, or both, that a given procedure or treatment is useful and effective
- Class II: Principle for which there is conflicting scientific evidence, a divergence of opinion, or both, about the usefulness, efficacy, or both, of a procedure or treatment
- Class IIa: Weight of evidence, opinion, or both, is in favor of the usefulness, efficacy, or both, of a procedure or treatment
- Class IIb: The usefulness, efficacy, or both, is less well established by means of evidence, opinion, or both, for a procedure or treatment
- Class III: Principle for which there is no sufficient scientific evaluation about the usefulness, efficacy, or both, of a procedure or treatment, in vitro studies, and animal studies

If a cardiac surgeon is to be convinced to critically assess his daily practice, more is generally required than advantages achieved by means of surrogate parameters. Therefore, we gave priority to studies analyzing different techniques or procedures with respect to patients' clinical outcomes (eg, mortality, morbidity, special organ function, transfusion requirements, length of stay at the intensive care unit, and overall hospital time; Table 1).

Table 1 contains a brief version of the questions formulated concerning CPB principles, scientific level of reviewed articles, selected clinical end points, and their classification on the basis of the scientific evidence. In case no scientific articles were available for a specific question, "not available" was indicated. The single results of the scientific level of the evaluated manuscripts are available on our Web site (address given in the appendix).

Table 3 depicts the selection of key words, their combination, and the number of articles identified in connection with our sample question regarding acid-base management in adults.

Results

A total of 33,000 articles identified were retrieved. Of these, 1500 articles fulfilled the criteria for the first step of the selection procedure. The 225 articles with the best scientific evidence available were classified according to the level of their scientific evidence on the basis of their methodological rigor. Table 1 depicts the scientific level of the evaluated literature.

Many studies showed methodological problems (eg, imprecise study design or inappropriate statistical methods). As a result, most of the classified articles showed divergent results regarding individual principles of CPB performance. Thus, the scientific evidence regarding CPB principles could not be conclusive in these cases.

Discussion

Since its first successful clinical application in 1953, the CPB technique has revolutionized cardiac surgery. Today, CPB is routinely used for various cardiac and noncardiac operations with good clinical results. Thus far no systematic review of the available literature has been undertaken to determine the amount and quality of scientific information. On the basis of our scientific evaluation of the current literature on 48 principles of CPB, not a single condition was of sufficient scientific merit to conclude that we were dealing with a principle for which there is clear evidence, scientific agreement, or both, that a given procedure or treatment is useful and effective.

Ideally, for each procedure or intervention, there should be direct and clear evidence from one or more studies that relate the application of this procedure (compared with specified alternatives) to the health outcomes of interest of a specific patient. However, rapid changes in medical practice, ethical considerations, and practical reasons make this desirable principle of patient care impossible to achieve. Thus, the limited scientific evaluation of current medical practice represents a general phenomenon and not one that is specific to the cardiothoracic surgical community.

Discussion of Our Sample Question

The sample question was, "What is the appropriate acid-base management for optimal cerebral protection in adults with respect to moderate respiratory deep hypothermia?"

The study design and content of 124 articles identified were reviewed. For 42 original contributions, the scientific value was assessed. Six articles were selected for classification of the scientific evidence on the question as to which pH-management strategy should be used for moderate hypothermia in adults.[12-17] Although study design and statistical evaluation revealed some shortcomings, 5 of the contributions achieved scientific level II.[12-16] From this, the conclusion could be drawn that alpha-stat management is associated with a decreased incidence of postoperative cerebral dysfunction without negatively affecting other organs in adult patients subjected to moderate hypothermia and prolonged CPB time.[13-16] This conclusion contrasted with data reported by Bashein and colleagues (scientific level II).[12] However, they used bubble oxygenators without arterial filters in their study, which may imply significant influencing factors. On the basis of the articles selected for review, the scientific evidence of this CPB principle was classified as IIa. Postoperative cerebral dysfunction is obviously affected by underlying patient comorbidity. Thus, whether our conclusion can be applied to patients with preexisting cerebrovascular disease or uncontrolled hypertension remains unclear, and the scientific background is lacking. Therefore, we do not believe that our conclusion can be used as a general recommendation. This demonstrates that basic elements of CPB performance do not meet evidence-based medicine criteria.

As for the question of which pH-management strategy should be applied to adults undergoing deep hypothermic arrest, no valid scientific data currently exist. We selected this example to demonstrate that there is a pressing need to apply evidence-based medicine principles to CPB performance.

Thousands of publications cover the issue of CPB performance. However, the quality of most articles in other medical journals does not meet basic scientific criteria.[18] After examining the quality of medical knowledge, other authors reported that only 15% of medical interventions are supported by solid scientific evidence.[19]

Although the quality of statistical analysis has improved and the application of more complex statistical procedures has increased during the past decades, imperfect study design and inadequate analysis remain an unresolved problem.[20] Articles now report larger numbers of analyzed cases than previously, yet the use of methods that aim to control type I error is rare.[21] True randomization requires exact evaluation of inclusion and exclusion criteria before a strata or blocked randomization protocol. In many publications the term "randomized" is used for clinical trial, although the investigation applied systematic allocation.[20] This condition limits the a priori scientific value of the study. For a scientific evaluation of CPB principles, more concise study designs and appropriate statistical evaluation seem to be mandatory.

Limitations of the Study

Dickersin and colleagues[22] examined the sensitivity and precision of Medline searches for randomized trials. They concluded that although the indexing terms available for searching Medline have improved, the sensitivity "still remains unsatisfactory."

For this study, the appropriate use, selection, and combination of Medical Subject Headings were cross-checked by two other members of our working group. In addition, currently available monographs dealing with the issue of CPB were reviewed for missing publications. All original contributions and reviews retrieved in our search were also checked for missing articles. However, we cannot exclude the possibility that important contributions failed to come to our attention.

In contrast to the Task Force Committee of the AHA and ACC, our purpose in undertaking this investigation could not be the development of guidelines for CPB performance for the following reasons:

1. Our Working Group on Extra-Corporeal Circulation does not have the logistic and personnel requirements available to the AHA/ACC committees.
2. For most CPB principles, the scientific background is not conclusive enough to allow general recommendations. Therefore, recommendations should be based on a consensus of numerous expert opinions on CPB in combination with a review of the literature.

We encourage our colleagues to improve the clinical results achievable with the application of CPB by expanding our limited knowledge of current practice using the criteria of evidence-based medicine. The scientific quality of CPB performance would improve if the societies of cardiothoracic surgeons could initiate large, prospective, randomized trials evaluating special CPB conditions.

David Eddy, professor of health policy and management at Duke University, who began his medical life as a cardiothoracic surgeon, became a leader in the field of evidence-based medicine, and trained other physicians to achieve consensus for medical practice, stated the following in 1991: "Get doctors to understand how much they need reliable information. What could be worse than two millennia spent making life and death decisions with inadequate information?"

We thank Dr Dagmar Luehmann, Department of Epidemiology, Medical University of Luebeck, for expert review of our article.

References

1. Audet AM, Greenfield S, Field M. Medical practice guidelines: current activities and future directions. *Ann Intern Med.* 1990;113:709-14.
2. Bonow RO, Carabello B, de Leon AC Jr, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation.* 1998;98:1949-84.
3. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 guidelines for coronary artery bypass graft surgery). *Circulation.* 1999;100:1464-80.
4. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *Circulation.* 1999;99:2829-48.
5. Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation.* 1998;97:501-9.
6. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol.* 2000;36:970-1062.
7. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA.* 1992;268:2420-5.
8. Cosgrove DM, Loop FD, Lytle BW, et al. Primary myocardial revascularization. Trends in surgical mortality. *J Thorac Cardiovasc Surg.* 1984;88:673-84.
9. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med.* 2001;344:395-402.
10. Govier AV, Reves JG, McKay RD, et al. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg.* 1984;38:592-600.
11. Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of Pa_{CO_2}. *Anesth Analg.* 1987;66:825-32.
12. Bashein G, Townes BD, Nessly ML, et al. A randomized study of carbon dioxide management during hypothermic cardiopulmonary bypass. *Anesthesiology.* 1990;72:7-15.
13. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. I. Mortality and cardiovascular morbidity. *J Thorac Cardiovasc Surg.* 1995;110:340-8.
14. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. *J Thorac Cardiovasc Surg.* 1995;110:349-62.
15. Venn GE, Patel RL, Chambers DJ. Cardiopulmonary bypass: perioperative cerebral blood flow and postoperative cognitive deficit. *Ann Thorac Surg.* 1995;59:1331-5.
16. Patel RL, Turtle MR, Chambers DJ, James DN, Newman S, Venn GE. Alpha-stat acid-base regulation during cardiopulmonary bypass improves neuropsychologic outcome in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 1996;111:1267-79.
17. Prough DS, Stump DA, Roy RC, et al. Response of cerebral blood flow to changes in carbon dioxide tension during hypothermic cardiopulmonary bypass. *Anesthesiology.* 1986;64:576-81.
18. Williamson JW, Goldschidt PG, Colton T. The quality of medical literature: an analysis of validation assessments. In: Bailar JC, Mosteller F, editors. Medical uses of statistics. Waltham (MA): NEJM Books; 1986.
19. Eddy DM, Billings J. The quality of medical evidence: implications for quality of care. *Health Aff (Millwood).* 1988;7:19-32.
20. Altman DG. Statistics in medical journals: developments in the 1980s. *Stat Med.* 1991;10:1897-913.
21. Smith R. The ethics of ignorance [editorial]. *J Med Ethics.* 1992;18:117-8, 134.
22. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ.* 1994;309:1286-91.

Appendix

The list of articles classified according to their scientific level can be found in the Internet at our Web site: www.herzchir.mu-luebeck.de.

Contributing Investigators

J. Babin-Ebell, MD, Klinik und Poliklinik für Herz- und Thoraxchirurgie der Universität Würzburg, Würzburg

C. Bartels, MD, Klinik für Herzchirurgie, Uniklinikum Lübeck, Lübeck

M. Bechtel, MD, Klinik für Herzchirurgie, Uniklinikum Lübeck, Lübeck

C. Benk, Herz- und Kreislaufzentrum der Albert-Ludwigs-Universität, Kardiotechnik, Freiburg

U. Boeken, MD, Klinik und Poliklinik für Thorax- und Kardiovaskuläre Chirurgie, Heinrich-Heine-Universität, Düsseldorf

S. Christiansen, MD, Klinik für Thorax-, Herz- und Gefäßchirurgie, Westfälische Wilhelms-Universität, Münster

J. Cleuziou, Klinik für Herz- und Thoraxchirurgie, Klinikum Wuppertal GmbH, Wuppertal

T. Doenst, MD, Herz- und Kreislaufzentrum der Albert-Ludwigs-Universität, Freiburg

H. Doerge, MD, Klinik für Thorax-, Herz- und Gefäßchirurgie, Universitätsklinik Aachen, Aachen

A. Erasmi, MD, Klinik für Herzchirurgie, Uniklinikum Lübeck, Lübeck

P. Feindt, MD, Klinik und Poliklinik für Thorax- und Kardiovaskuläre Chirurgie, Heinrich-Heine-Universität, Düsseldorf

A. Gerdes, MD, Klinik für Herzchirurgie, Uniklinikum Lübeck, Lübeck

T. Hanke, Klinik für Herzchirurgie, Uniklinikum Lübeck, Lübeck

M. Heiermann, MD, Herzzentrum Wuppertal, Herz- und Thoraxchirurgie, Klinikum, Wuppertal GmbH, Wuppertal

S. Johannsson, MD, Herz- und Kreislaufzentrum der Albert-Ludwigs-Universität, Freiburg

E. Joubert-Hübner, Klinik für Herzchirurgie, Kardiotechnik, Uniklinikum Lübeck, Lübeck

M. Kemper, MD, Herz- und Kreislaufzentrum der Albert-Ludwigs-Universität, Freiburg
J. L. Kobba, MD, Herz- und Kreislaufzentrum der Albert-Ludwigs-Universität, Freiburg
M. Krause, Herz- und Kreislaufzentrum der Albert-Ludwigs-Universität, Kardiotechnik, Freiburg
A. Markewitz, MD, Abteilung für Kardiochirurgie, Bundeswehrkrankenhaus Koblenz, Koblenz
J. Martin, MD, Herz- und Kreislaufzentrum der Albert-Ludwigs-Universität, Freiburg
G. Matheis, MD, Klinikum der Wolfgang-Goethe-Universität, Klinik für Thorax,- Herz- und Gefäßchirurgie, Frankfurt
U. Mehlhorn, MD, Klinik und Poliklinik für Herz- und Thoraxchirurgie, Universität Köln, Köln
M. Misfeld, MD, Klinik für Herzchirurgie, Uniklinikum Lübeck, Lübeck
Dip. Biol. M. Misoph, Klinik und Poliklinik für Herz- und Thoraxchirurgie der Universität Würzburg, Würzburg
A. Nötzold, MD, Klinik für Herzchirurgie, Uniklinikum Lübeck, Lübeck
S. Pascucci, MD, Herzzentrum Bad Krozingen, Bad Krozingen
A. Philipp, MD, Klinik und Poliklinik für Herz-, Thorax- und herznahe Gefäßchirurgie, Klinikum der Universität Regensburg, Regensburg
W. Reents, MD, Klinik und Poliklinik für Herz- und Thoraxchirurgie der Universität Würzburg, Würzburg
J. Roetker, MD, Klinik für Thorax-, Herz- und Gefäßchirurgie, Westfälische Wilhelms-Universität, Münster
C. Schlensak, MD, Herz- und Kreislaufzentrum der Albert-Ludwigs-Universität, Freiburg
F.-X. Schmid, MD, Klinik und Poliklinik für Herz-, Thorax- und herznahe Gefäßchirurgie, Klinikum der Universität Regensburg, Regensburg
T. Tirilomis, MD, Klinik für Thorax-, Herz- und Gefäßchirurgie, Universitätsklinik Göttingen, Göttingen
D. Troitzsch, MD, Klinik für Herzchirurgie, Klinikum der Phillips-Universität, Marburg
A. Sam Sirath, Klinik für Herzchirurgie, Klinikum der Phillips-Universität, Marburg
H. Vetter, MD, Klinik für Herz- und Thoraxchirurgie, Klinikum Wuppertal GmbH, Wuppertal
C. Vicol, MD, Herzchirurgische Klinik Zentralklinikum, Augsburg
S. Vogt, MD, Klinik für Herzchirurgie, Klinikum der Phillips-Universität, Marburg.